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(54) Abstract Title
Pharmaceutical compositions comprising the cannabinoids THC and CBD

(57) Pharmaceutical compositions comprising cannabinoids having specific ratios of cannabidiol (CBD) to tetrahydrocannabinol (THC). The compositions are clinically useful in the treatment or management of specific diseases or medical conditions.

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PHARMACEUTICAL COMPOSITIONS

Cannabis has been used medicinally for many years, and in Victorian times was a widely used component of prescription medicines. It was used as a hypnotic sedative for the treatment of "hysteria, delirium, epilepsy, nervous insomnia, migraine, pain and dysmenorrhoea". The use of cannabis continued until the middle of the twentieth century, and its usefulness as a prescription medicine is now being re-evaluated. The discovery of specific cannabinoid receptors and new methods of administration have made it possible to extend the use of cannabis-based medicines to historic and novel indications.

The recreational use of cannabis prompted legislation which resulted in the prohibition of its use. Historically, cannabis was regarded by many physicians as unique; having the ability to counteract pain resistant to opioid analgesics, in conditions such as spinal cord injury, and other forms of neuropathic pain including pain and spasm in multiple sclerosis.

In the United States and Caribbean, cannabis grown for recreational use has been selected so that it contains a high content of tetrahydrocannabinol (THC), at the expense of other cannabinoids. In the Merck Index (1996) other cannabinoids known to occur in cannabis such as cannabidiol and cannabinol were regarded as inactive substances. Although cannabidiol was formerly regarded as an inactive constituent there is emerging evidence that it has pharmacological activity, which is different from that of THC in several respects. The therapeutic effects of cannabis cannot be satisfactorily explained just in terms of one or the other 'active' constituents. It has been shown that tetrahydrocannabinol (THC) alone produces a lower degree of pain relief than the same quantity of THC given as an extract of cannabis. The pharmacological basis underlying this phenomenon has been investigated. In some cases, THC and cannabidiol (CBD) have pharmacological properties of opposite effect in the same preclinical tests, and the same effect in others. For example, in some clinical studies and from anecdotal reports there is a perception that CBD modifies the psychoactive effects of THC. This spectrum of activity of the two cannabinoids may help to explain some of the therapeutic benefits of cannabis grown in different regions of the world. It also points to useful effects arising from combinations of THC and CBD. These have been investigated by the applicant. **Table 1** below shows the difference in pharmacological properties of the two cannabinoids.

Table 1

Effect	THC	THCV	CBD	CBDV	Reference
CB_1 (Brain receptors)	++		±		Pertwee *et al*, 1998
CB_2 (Peripheral receptors)	+		-		
CNS Effects					
Anticonvulsant †	–		++		Carlini *et al*, 1973
Antimetrazol	-		-		GW Data
Anti-electroshock	-		++		GW data
Muscle Relaxant	--		++		Petro, 1980
Antinociceptive	++		+		GW data
Catalepsy	++		++		GW data
Psychoactive	++		-		GW data
Antipsychotic	-		++		Zuardi *et al*, 1991
Neuroprotective antioxidant activity*	+		++		Hampson A J *et al*, 1998
Antiemetic	++		-		
Sedation (reduced spontaneous activity)	+		+		Zuardi *et al*, 1991
Appetite stimulation	++				
Appetite suppression			++		
Anxiolytic	-		++		GW data
Cardiovascular Effects					
Bradycardia	-		+		Smiley *et al*, 1976
Tachycardia	+		-		
Hypertension §	+		-		
Hypotension §	-		+		Adams *et al*, 1977
Anti-inflammatory	±		±		Brown, 1998
Immunomodulatory/anti-inflammatory activity					
Raw Paw Oedema Test	-		++		GW data
Cox 1					GW data
Cox 2					GW data
TNFá Antagonism	+	+	++	++	
Glaucoma	++		+		

* Effect is CB1 receptor independent.

† THC is pro convulsant

§ THC has a biphasic effect on blood pressure; in naïve patients it may produce postural hypotension and it has also been reported to produce hypertension on prolonged usage. GW Internal Report No 002/000159.

From these pharmacological characteristics and from direct experiments carried out by the applicant it has been shown, surprisingly that, combinations of THC and CBD in varying proportions are particularly useful in the treatment of certain therapeutic conditions. It has further been found clinically that the toxicity of a mixture of THC and CDB is less than that of THC alone.

Accordingly, in it's first aspect the present invention provides pharmaceutical compositions comprising cannabinoids which have specific ratios of CBD to THC, which have been found to be clinically useful in the treatment or management of specific diseases or medical conditions.

In the second of its aspects the invention also provides pharmaceutical compositions which have specific ratios of tetrahydrocannabinovarin (THCV) or cannabidivarin (CBDV). THCV and CBDV are known cannabinoids which are predominantly expressed in particular Cannabis plant varieties and it has been found that THCV has qualitative advantageous properties compared with THC and CBD respectively. Subjects taking THCV report that the mood enhancement produced by THCV is less disturbing than that produced by THC. It also produces a less severe hangover.

In a third aspect the invention provides pharmaceutical compositions which have specific ratios of THCV to THC. Such compositions have been found to be particularly useful in the field of pain relief and appetite stimulation.

The invention also provides methods of making the aforementioned pharmaceutical compositions as well as methods of using them to treat or manage specific diseases or conditions. Embodiments of compositions, methods and uses of the present invention are set out in the accompanying claims.

It has particularly been observed by the present applicants that the combinations of the specific cannabinoids are more beneficial than any one of the individual cannabinoids alone. Preferred

embodiments are those compositions in which the amount of CBD is in a greater amount by weight than the amount of THC. Such compositions are designated as 'reverse-ratio' compositions and are novel and unusual since, in the various varieties of medicinal and recreational Cannabis plant available world-wide, CBD is the minor cannabinoid component compared to THC. In other embodiments THC and CBD or THCV and CBDV are present in approximately equal amounts or THC or THCV are the major component and may be up to 95.5% to just 5%CBD.

Particularly preferred embodiments and the target medical conditions for which they are suitable are shown in **Table 2** below.

Table 2: **Target Therapeutic Groups for Different Ratios of Cannabinoid**

Product group	Ratio THC:CBD	Target Therapeutic Area
High THC	>95:5	Cancer pain, migraine, appetite stimulation
Even ratio	50:50	Multiple sclerosis, spinal cord Injury, peripheral neuropathy, other neurogenic pain.
Reverse/Broad ratio CBD	<25:75	Rheumatoid arthritis, Inflammatory bowel diseases.
High CBD	<5:95	Psychotic disorders (schizophrenia), Epilepsy & movement disorders Stroke, head injury, Disease modification in RA and other inflammatory conditions Appetite suppression

The pharmaceutical compositions of the invention may be formulated from pure cannabinoids in combination with pharmaceutical carriers and exipients which are well-known to those skilled in the art. For example CBD and THC can be purchased from Sigma-Aldrich Company Ltd, Fancy Road, Poole Dorset, BH12 4QH. CBDV and THCV may be extracted from Cannabis plants using techniques well-known to those skilled in the art. Working with Cannabis plants and cannabinoids may require a government licence in some territories but governments readily

make such licences available to parties who apply for the purposes of medicinal research and commercial development of medicines. In the UK a licence may be obtained from the Home Office.

In preferred embodiments of the invention the compositions comprise extracts of one or more varieties of whole Cannabis plants, particularly *Cannabis sativa, Cannabis indica* or plants which are the result of genetic crosses, self-crosses or hybrids thereof. The precise cannabinoid content of any particular cannabis variety may be qualitatively and quantitatively determined using methods well known to those skilled in the art such as TLC or HPLC. Thus, one may chose a Cannabis variety from which to prepare an extract which will produce the desired ratio of CBD to THC or CBDV to THCV or THCV to THC. Alternative extracts from two of more different varieties may be mixed or blended to produce a material with the preferred cannabinoid ratio for formulating into a pharmaceutical composition.

The preparation of convenient ratios of THC- and CBD-containing medicines is made possible by the cultivation of specific chemovars of cannabis. These chemovars (varieties distinguished by the cannabinoids produced, rather than the morphological characteristics of the plant) can be been bred by a variety of plant breeding techniques which will be familiar to a person skilled in the art. Propagation of the plants by cuttings for production material ensures that the genotype is fixed and that each crop of plants contains the cannabinoids in substantially the same ratio.

Furthermore, it has been found that by a process of horticultural selection, other chemovars expressing their cannabinoid content as predominantly tetrahydrocannabinovarin (THCV) or cannabidivarin (CBDV) can also be achieved.

Horticulturally, it is convenient to grow chemovars producing THC, THCV, CBD and CBDV as the predominant cannabinoid from cuttings. This ensures that the genotype in each crop is identical and the qualitative composition (the proportion of each cannabinoid in the biomass) is the same. From these chemovars, extracts can be prepared by the similar method of extraction. Convenient methods of preparing primary extracts include maceration, percolation, extraction with solvents such as C1 to C5 alcohols (ethanol), Norflurane (HFA134a), HFA227 and liquid carbon dioxide under pressure. The primary extract may be further purified for example by

supercritical or subcritical extraction, vaporisation and chromatography. When solvents such as those listed above are used, the resultant extract contains non-specific lipid-soluble material. This can be removed by a variety of processes including chilling to -20°C followed by filtration to remove waxy ballast, extraction with liquid carbon dioxide and by distillation. Preferred plant cultivation and extract preparation methods are shown in the Examples. The resulting extract is suitable for incorporation into pharmaceutical preparations. Methods of administration may be based on sublingual drops, sublingual tablets, gels and sprays, aerosol inhalations, vaporisers, other conventional pharmaceutical oral dosage forms, enemas and rectal suppositories. Other possible formulations are recited in the accompanying claims.

There are advantages and disadvantages attaching to each of these routes of administration. In general, preparations administered via the respiratory tract, oral/nasal tract and the distal rectum avoid the hepatic first pass effect. Medicaments swallowed are subject to substantial metabolism during their first pass through the liver, and the pattern of metabolites produced may vary according to the route of administration.

There are a number of therapeutic conditions which may be treated effectively by cannabis. The proportion of different cannabinoids in such preparations determines the specific therapeutic conditions which are best treated, and the present invention addresses the formulations which are most suitable for this purpose. As aforesaid the teaching of the invention is illustrated by the use of preparations containing specific ratios of cannabinoid (**Table 2**), and is further illustrated by the examples.

By direct experiment, it has been shown that administration of CBD (or CBDV) before the administration of THC modifies the cognitive effects experienced. The psychoactive effects of THC are diminished, and subsequent sedation is postponed and mitigated. This reduction is not observed if the THC is given before CBD. Accordingly, one preferred embodiment of the invention is a tablet for buccal or sublingual administration that has a rapidly soluble layer of CBD or CBDV, and a second layer or core of less rapidly soluble THC or THCV. The formulation thus provides a means of making medicaments available for absorption in a timed sequence. Indeed a variety of compositions having modified release profiles which comprise at least two phases can be formulated.

It is a further observation of the present applicants that CBD is able to act as a pharmaceutical stabilizer of pharmaceutical compositions and thus prolong shelf-life. Without being bound by theory it is thought that this may be due to anti-oxidant properties of CBD. Although its anti-oxidant properties are known to be useful in a pharmacological setting in relation to living matter, its effects as a pharmaceutical stabilizer have not previously been observed.

Accordingly, in another of it's aspects the invention relates to the use of CBD to extend the shelf-life of a pharmaceutical product which comprises one or more biologically active components. Preferred biologically active components are set forth in the accompanying claims and may be one or more of the classes of medicaments and specific medicaments shown in **Table 3** below:

Table 3

CLASS OF MEDICAMENT	EXAMPLE OF MEDICAMENT
Alkaloid-rich extracts of *Belladonna atropa*	Hyoscine Hyoscymine Atropine
Alkaloid-rich extracts of *Gallanthus spp.*	
Alkaloid-rich extracts of *Narcissus spp.*	
Alkaloid-rich extracts of opium	Morphine Codeine Diamorphine
Alkaloid-rich extracts of Pilocarpine	Pilocarpine salycilate
Anti-asthmatics	Terbutaline
Antibacterials	
Antifungals	Fluconazole
Anti-inflammatory agents	Benzidamine Pyroxicam
Antivirals	Acyclovir Zidovudine
Beclomethasone	
Cannabinoid-rich fractions of *Cannabis sativa* and *Cannabis indica*, and chemovars derived from them	
Cannabinoids	Δ^{-9} Tetrahydrocannabinol (THC) THCV Cannabinol (CBN)
Cannbinoid-rich fractions containing cannabinoids	

other than THC, CBD or CBN as the most abundant component	
Cardiovascular Agents	Nifedipine Diltiazem Verapamil
Centrally acting analgesics	Butorphenol Buprenorphine Fentanyl
Fluticasone proprionate	
Polyunsaturated fatty acid triglycerides	n-3 and n-6 PUFAs Acylglycerols
Sympathomimetic amines	Salbutamol

The invention will now be further described with reference to the following non-limiting Examples:

Example1

Growing of Medicinal Cannabis

Plants are grown as clones from germinated seed, under glass at a temperature of 25°C ± 1.5°C for 3 weeks in 24 hour daylight; this keeps the plants in a vegetative state. Flowering is induced by exposure to 12 hour day length for 8-9 weeks.

No artificial pesticides, herbicides, insecticides or fumigants are used. Plants are grown organically, with biological control of insect pests.

The essential steps in production from seed accession to dried Medicinal Cannabis are summarised as follows:

Seed Accessions

↓

Seeds germinated at G-Pharm (UK)

↓

Selection for cannabinoid content and vigour

↓

Mother Plant

↓

Cutting s rooted

14-21 days in peat plug

25 °C, 24 hour day length

↓

Rooted cuttings potted up in 5 litre pots of bespoke compost

↓

Young Clone Plant established

3 weeks, 24 hour day length, 25 °C

↓

Lower Branches Removed end of week 3

Used to make new generation of cuttings

↓

Induction of flowering

Plant relocation to 12 hour day length are to induce flowering

↓

Flower formation and maturation

8-9 weeks at 25 °

↓

Harvest

90% of flowers and leaves senesced

↓

Drying

Under conditions of light exclusion

↓

MEDICINAL CANNABIS

Example 2

Determination of Cannabinoid Content in Plants and Extracts

Identity by TLC

a) Materials and methods

Equipment	Application device capable of delivering an accurately controlled volume of solution i.e 1μl capillary pipette or micro litre syringe.
	TLC development tank with lid
	Hot air blower
	Silica gel G TLC plates (SIL N-HR/UV254), 200μm layer with fluorescent indicator on polyester support.
	Dipping tank for visualisation reagent.
Mobile phase	80% petroleum ether 60:80/20% Diethyl ether.
Visualisation reagent	0.1% w/v aqueous Fast Blue B (100mg in 100ml de-ionised water). An optional method is to scan at UV 254 and 365 nm.

b) Sample preparation

i) Herbal raw material

Approximately 200mg of finely ground, dried cannabis is weighed into a 10ml volumetric flask. Make up to volume using methanol:chloroform (9:1) extraction solvent.

Extract by ultrasound for 15 minutes. Decant supernatant and use directly for chromatography.

ii) Herbal drug Extract

Approximately 50mg of extract is weighed into a 25ml volumetric flask. Make up to volume using methanol solvent. Shake vigorously to dissolve and then use directly for chromatography.

c) Standards

0.1 mg/ml delta-9-THC in methanol (THC certificate of analysis given on page 17).
0.1 mg/ml CBD in methanol.(CBD certificate of analysis on page 18).

The standard solutions are stored frozen at -20°C between uses and are used for up to 12 months after initial preparation.

d) Test solutions and method

Apply to points separated by a minimum of 10mm.

i) either 5μl of herb extract or 1μl of herbal extract solution as appropriate.
ii) 10μl of 0.1 mg/ml delta-9-THC in methanol standard solution
iii) 10μl of 0.1mg/ml CBD in methanol standard solution

Elute the TLC plate through a distance of 8cm, then remove the plate. Allow solvent to evaporate from the plate and then repeat the elution for a second time (double development).

The plate is briefly immersed in the Fast Blue B reagent until the characteristic re/orange colour of cannabinoids begins to develop. The plate is removed and allowed to dry under ambient conditions in the dark.

A permanent record of the result is made either by reproduction of the image by digital scanner(preferred option) or by noting spot positions and colours on a tracing paper.

Assay THC, THCA, CBD, CBDA and CBN by HPLC

a) Materials and methods

Equipment:	HP 1100 hplc with diode array detector and autosampler. The equipment is set up and operated in accordance with in-house standard operating procedures (SOPlab037)
HPLC column	Discovery C8 5μm, 15x 0.46 cm plus Kingsorb ODS2 precolumn 5μm 3 x 0.46 cm.
Mobile Phase	Acetonotrile: methanol: 0.25% aqueous acetic acid (16:7:6 by volume)
Column Operating Temperature	25°C
Flow Rate	1.0 ml/min
Injection Volume	10μl
Run time	25mins
Detection	Neutral and acid cannabinoids 220nm (band width 16nm) Reference wavelength 400nm/bandwidth 16nm
	Slit 4nm
	Acid cannabinoids are routinely monitored at 310nm (band width 16nm)

for qualitative confirmatory and identification purposes only.

Data capture HP Chemistation with Version A7.01 software

b) Sample preparation

Approximately 40mg of Cannabis Based Medicinal Extract is dissolved in 25ml methanol and this solution is diluted to 1 to 10 in methanol. This dilution is used for chromatography.

0.5 ml of the fill solution, contained within the Pump Action Sublingual Spray unit, is sampled by glass pipette. The solution is diluted into a 25ml flask and made to the mark with methanol. 200μl of this solution is diluted with 800 μl of methanol.

Herb or resin samples are prepared by taking a 100mg sample and treating this with 5 or 10ml of Methanol/Chloroform (9/1 w/v). The dispersion is sonicated in a sealed tube for 10 minutes, allowed to cool and an aliquot is centrifuged and suitably diluted with methanol prior to chromatography

c) Standards

External standardisation is used for this method. Dilution of stock standards of THC, CBD and CBN in methanol or ethanol are made to give final working standards of approximately accurately 0.1 mg/ml. The working standards are stored at - 20°C and are used for up to 12 months after initial preparation.

Injection of each standard is made in triplicate prior to the injection of any test solution. At suitable intervals during the processing of test solutions, repeat injections of standards are made. In the absence of reliable CBDA and THCA standards, these compounds are analysed using respectively the CBD and THC standard response factors.

The elution order has been determined as CBD, CBDA, CBN, THC and THCA. Other cannabinoids are detected using this method and may be identified and determined as necessary.

d) Test solutions

Diluted test solutions are made up in methanol and should contain analytes in the linear working range of 0.02-0.2 mg/ml.

e) Chromatography Acceptance Criteria:

The following acceptance criteria are applied to the results of each sequence as they have been found to result in adequate resolution of all analytes (including the two most closely eluting analytes CBD and CBDA)

i) Retention time windows for each analyte:

CBD 5.4-5.9 minutes
CBN 7.9-8.7 minutes
THC 9.6-10.6 minutes

ii) Peak shape (symmetry factor according to BP method)

CBD < 1.30
CBN < 1.25
THC < 1.35

iii) A number of modifications to the standard method have been developed to deal with those samples which contain late eluting impurity peaks e.g method CBD2A extends the run time to 50 minutes. All solutions should be clarified by centrifugation before being transferred into autosampler vials sealed with teflon faced septum seal and cap.

iv) The precolumn is critical to the quality of the chromatography and should be changed when the back pressure rises above 71 bar and/or acceptance criteria regarding retention time and resolution, fall outside their specified limits.

f) Data Processing

Cannabinoids can be subdivided into neutral and acidic- the qualitative identification can be performed using the DAD dual wavelength mode. Acidic cannabinoids absorb strongly in the region of 220nm-310nm. Neutral cannabinoids only absorb strongly in the region of 220nm.

Routinely, only the data recorded at 220 nm is used for quantitative analysis.

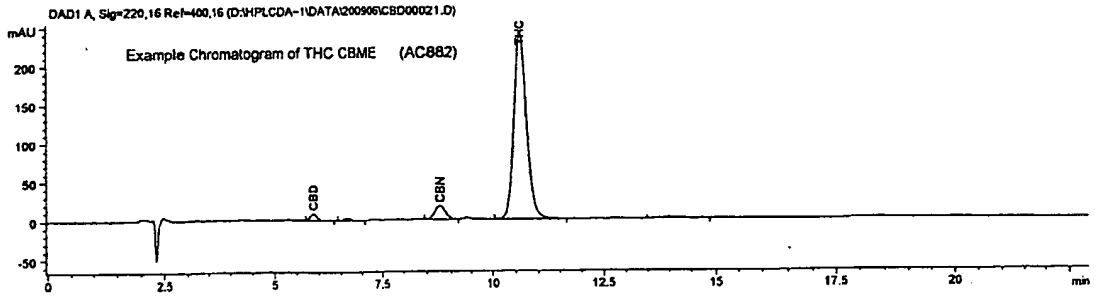
The DAD can also be set up to take UV spectral scans of each peak, which can then be stored in a spectral library and used for identification purposes.

Data processing for quantitation utilises batch processing software on the Hewlett Packard Chemstation.

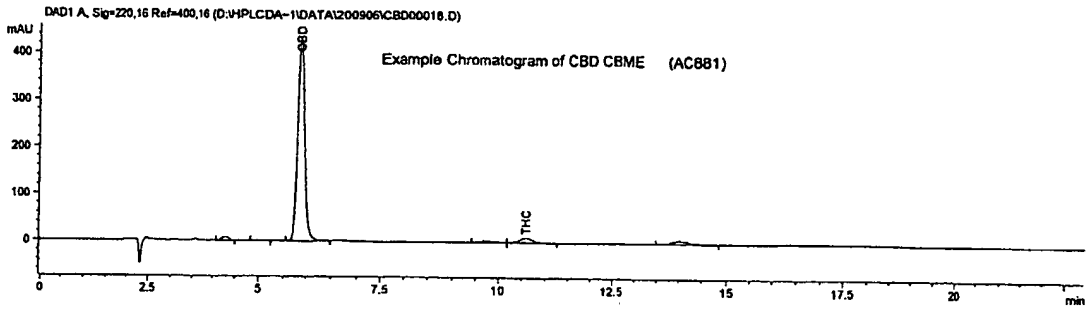
a) Sample Chromatograms

HPLC sample chromatograms are provided below, for THC and CBD Herbal Drug extracts.

CBME THC



CBME CBD



Example 3

Preparation of the Herbal Drug Extract

A flow chart showing the process of manufacture of extract from the High-THC and High-CBD chemovars is given below:

Medicinal Cannabis (High-THC or High-CBD)

↓

Chopping to predominantly 2 to 3mm

↓

Heating at 100 to 150°C for sufficient time to decarboxylate acid form of cannabinoids to produce neutral cannabinoids

↓

Extraction with a specified volume of liquid carbon dioxide over 6 to 8 hours

↓

Removal of CO_2 by depressurisation to recover crude extract

↓

"Winterisation"-Dissolution of crude extract in ethanol Ph. Eur. followed by chilling solution (-20°C/48 hrs) to precipitate unwanted waxes

↓

Removal of unwanted waxy material by cold filtration

↓

Removal of ethanol from the filtrate by
thin film evaporation under reduced pressure

Example 4

High THC cannabis was grown under glass at a mean temperature of 21 + 2°C, RH 50 – 60%. Herb was harvested and dried at ambient room temperature at a RH of 40 – 45% in the dark. When dry, the leaf and flower head were stripped from stem and this dried biomass is referred to as 'medicinal cannabis'.

Medicinal cannabis was reduced to a coarse powder (particles passing through a 3 mm mesh) and packed into the chamber of a Supercritical Fluid Extractor. Packing density was 0.3 and liquid carbon dioxide at a pressure of 600 bar was passed through the mass at a temperature of 35°C. Supercritical extraction is carried out for 4 hours and the extract was recovered by stepwise decompression into a collection vessel. The resulting green-brown oily resinous extract is further purified. When dissolved in ethanol BP (2 parts) and subjected to a temperature of -20°C for 24 hours a deposit (consisting of fat-soluble, waxy material) was thrown out of solution and was removed by filtration. Solvent was removed at low pressure in a rotary evaporator. The resulting extract is a soft extract which contains approximately 60% THC and approximately 6% of other cannabinoids of which 1 – 2 % is cannabidiol and the remainder is minor cannabinoids including cannabinol. Quantitative yield was 9% w/w based on weight of dry medicinal cannabis.

A high CBD chemovar was similarly treated and yielded an extract containing approximately 60% CBD with up to 4% tetrahydrocannabinol, within a total of other cannabinoids of 6 % Extracts were made using THCV and CBDV chemovars using the general method described above.

A person skilled in the art will appreciate that other combinations of temperature and pressure (in the range +10°C to 35°C and 60 – 600 bar) can be used to prepare extracts

under supercritical and subcritical conditions.

Example 5

Street cannabis (marijuana) grown in the US and Caribbean typically has a high pecentage of total cannabinoid as THC; European (usually described as 'Moroccan' cannabis) contains approximately equal quantities of THC and CBD. This may account for conflicting reports on the efficacy of cannabis in certain clinical studies. The applicant has sought to introduce precision in producing defined ratios of cannabinoid in two ways; by using mixtures of defined extracts and also by producing an extract from a single chemovar which produces the appropriate ratio of cannabinoids. Chemovars which express their cannabinoid content as predominantly one compound have been used to prepare the compositions of the invention but the teaching of the patent can be applied to synthetically produced cannabinoids or cannabinoids obtained by purification of cannabis

Certain chemovars express an approximately 50 : 50 ratio of THCV/CBDV. It is therefore convenient to use a single plant extract to provide the ratio of cannabinoids. When the plants are grown from cuttings, the genotype is fixed and the ratio of cannabinoids is a constant. The overall yield may vary but this is factored into the quantity of extract used to provide a defined quantity of cannabinoid. A formulation which is particularly suitable for the treatment of multiple sclerosis is made to the following formula:

CBME extract of chemovar G10 providing

	5a	**5b**	**5c**
THCV	0.1	2.5	10 parts
CBDV	0.1	2.5	10 parts
Spray-dried lactose	60	60	50 parts
Dextrates	37.7 parts	21.5	16.5
Lecithin	1	10	10 parts
α-tocopherol	0.1	2.5	2.5 parts
Magnesium stearate	1	1	1 part

The CBME-G10 extract is dissolved in 5 parts of ethanol and this solution used to mass the other ingredients. The mass is forced through a sieve, and the granules are dried at low temperature. When dry, the granules are dusted with magnesium stearate and compressed to 1.5 Newtons to give tablets suitable for sublingual administration to patients with multiple sclerosis, spinal chord injury, peripheral neuropathy or other neurogenic pain.

Example 6

In order to make cannabidiol available before THC, a multi layered dosage form has been made. In this exemplification, THC obtained either from synthetic or natural sources is contained in a core. CBD obtained from a natural source such as a cannabis chemovar extract or from synthetic material is present in the outer coating, which dissolves first and is followed by THC.

A two-layered tablet is formulated from the following ingredients.

Inner Core

CBME-G1 providing THC	2 part
Direct compression lactose	66.9 parts
Pre-gelatinised starch	30 parts
α-tocopherol	0.1 part
Magnesium stearate	1 part

The CBME is dissolved in sufficient ethanol for the whole to be sprayed onto the other dry ingredients. The powder is allowed to dry at room temperature and thoroughly mixed. Magnesium stearate is added and the tablets are compressed to a hardness of 6 Newtons. These cores can be pressed conveniently in a tablet press with 7mm biconvex dies. When tested in a BP-type disintegration apparatus, disintegration time of these core tablets was 5 – 10 minutes.

Outer Layer

The outer layer of tablets was prepared from the following ingredients:

CBME-G5	8 parts
Glycerol monostearate	5 parts
Lecithin	5 parts
Direct compression lactose	55 parts
Pre-gelatinised starch	26.7parts
α-tocopherol	0.2 parts
Oil of Peppermint	0.1 part

Sufficient ethanol BP is used to dissolve the CBME extract which is then sprayed on to the other dry ingredients. Ethanol is allowed to evaporate at room temperature and the dry granules are thoroughly mixed and tableting arranged so that half of the charge is delivered into a 9mm table die. The charge is lightly compressed (0.25 Newtons), a core as described above is added to each die, and the remainder of the tablet granules added to the die. Tablets are compressed to a hardness of 1.5 Newtons.

The tablets so produced have a soft outer coat which is compressed sufficiently hard to withstand limited handling, and are individually packed in blister packs to reduce friability. When the tablet is placed under the tongue, the soft outer core quickly disintegrates and forms a slightly gelatinous mass which yields CBD. The disintegration of this coating when tested in a BP model disintegration apparatus is 1 – 4 minutes. The harder core containing THC then dissolves and then yields THC for absorption after CBD has already been presented to the sublingual or buccal mucosae. By using a two-layered tablet in this way it is possible to optimise the sequence of presentation of cannabinoids. CBD absorbed first has an *in vitro* and *in vivo* antioxidant activity which is beneficial in enhancing the stability of THC and aiding its absorption. As the CBD component of the extract used to supply the THC component contains relatively small amounts of CBD which would act as antioxidant, additional tocopherol is included to act as chemical antioxidant. The tablets so produced are useful in the treatment of multiple sclerosis and other neurogenic pains.

The same tablet mix when compressed to a hardness of 6 Newtons is also suitable for the treatment of rheumatoid arthritis and other inflammatory bowel diseases when given as an oral preparation intended to be swallowed.

Surprisingly, although it is reported that cannabis stimulates appetite, it has been shown by direct experiment that High CBD extracts decrease the food intake and weight gain of mice. The High CBD formulation is therefore useful as a means of reducing appetite in humans.

Example 7

A specific chemovar (designated G9) produces two principal cannabinoids; THCV : THC in the ratio 85 : 15. This chemovar produces relatively little CBD and this exemplifies the extreme of the high THC:Cbd ratios. THCV produces a more rapid analgesic effect than THC, with reduced potential for hangover. A pharmaceutical preparation prepared from this extract is therefore desirable for the treatment of opioid-resistant pain where a rapid onset of action is required. A sublingual spray formulation has the following formula.

CBME-G9 extract providing

THCV	85 parts
THC	15 parts
Cremophore RH40	300 parts
α-tocopherol	1 part
Ethanol BP to produce	1,000 parts

The ingredients are dissolved in the ethanol and dispensed in 10ml quantities into a glass vial, closed with a pump action spray break-up button. Each 1ml of product contains 100mg of cannabinoid, and each actuation of the pump delivers 100 µl in a fine spray which is directed to the area of mucosae under the tongue.

This preparation is used as part of the treatment for patients suffering from migraine, cancer pain and multiple sclerosis.

Example 8

A formulation as described in the preceding example is made up substituting CBME-G5 (high CBD). This spray can be used to prime patients by giving a dose of CBD 5 – 10 minutes before administration of the high THC/THCV formulation.

Proprietary, two-compartment/double pressure buttons are available, and a composite package contains solution as described in this and the preceding example. The availability of the two sublingual solutions in a convenient package allows the patient to titrate the dose of either component to optimise the therapeutic effect required.

The antioxidant effect of CBD *in vitro* is demonstrated by the following assay levels after storage at 5 ± 3°C. The data are reported as percentage of initial assay value.

Table 4: **Stability Data for High THC and High CBD and Even Ratio CBD/THC, Pump Action Sublingual Spray (PASS), and Sublingual Tablets**

FORMULATION	ASSAY VALUE AFTER ELAPSED TIME			
	3 months (Range)		6 months (Range)	
	THC	CBD	THC	CBD
PASS				
High THC	98.2 (95.6– 100.4)		95.6 (93.7 – 98.5)	
High CBD		100.6 (99.7 – 101.6)	101.0 (98.3 – 103.6)	
Even Ratio THC : CBD	99.5 (98.3 – 101.5)	101.2 100.3 – 102.0	100.4 (99.3 – 102.8)	104.5 193.5 – 106.5
SUBLINGUAL TABLETS STORED AT 5°C				
High THC (2mg)	89.4			
High CBD (2mg)		99.0		
Even Ratio	95.5	99.0		

It is clear from the table above that CBD in this formulation has good stability, whereas THC is less stable. A preparation containing both CBD and THC in the concentrations which are of therapeutic interest appears to have a protective action and enhances the stability of the even ratio spray and tablet products.

The examples given above illustrate the teaching of the patent, and it will be clear to one skilled in the art that elements from the different formulations can be adapted to produce a wide range of formulations. These are suitable for treatment of a range of therapeutic indications. Elements may be taken from any of the above examples to produce a specific formulation with the desired speed of onset and duration of action within the limits described.

Example 9

Cannabinoids are known to be useful in the treatment of inflammatory bowel disease. However, the amount of cannabinoid reaching the lower bowel (distal ileum and colon) is unknown. Enemas are suitable for local application of inflamed bowel. The following formulation is based on a foaming enema and provides a broad ratio combination of cannabinoids for local application.

CBME-G1 providing THC	4 mg
CBME-G5 providing CBD	20mg
Docusate sodium	100mg
Glycerol monostearate	2.5gm
Carboxymethylcellulose	250mg
Water	250ml

The CBME extracts are dissolved in the ingredients and mixed in the order indicated above. A 50ml quantity is dispensed into a compressible plastic container fitted with a 150ml enema nozzle with a terminal bulb. Before use, the container is shaken vigorously to produce a foam. The foam is injected by the nozzle and the quantity of foam produced travels typically for 1 – 2 metres into the lower bowel. The foam is compressible and

produces minimal discomfort to the patient compared with non-compressible enemas. The method of treatment can be combined with steroids given either systemically or as an enema for treatment of inflammatory bowel disease.

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REFERENCES

Adams M.D. *et al* (1977)
A Cannabinoid with Cardiovascular Activity but no Overt Behavioural Effects
Experientia, **33**, 1204-1205

Burstein S. and Raz A. (1972)
Inhibition of prostaglandin E2 biosynthesis by D1-tetrahydrocannabinol. Prostaglandins 2 :369-375.

Ed. Brown D.T, 207
Cannabis 'The Genus *Cannabis*'

Carlini E.A., Leiter J.R., Tannhauser M. and Berardi A.C. (1973) Cannabidiol and *Cannabis sativa* Extract Protect Mice and Rats Against Convulsive Agents
J. Pharm. Pharmacol **25**, 664-665

Davis K H Jr., McDaniel I A Jr., et al
Some Smoking Characteristics of Marijuana Cigarettes.
The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects
Academic Press, Inc. (1984)

De Meijer E.P.M. and Keizer L.C.P. (1996)
Patterns of diversity in *Cannabis. Genetic Resources and Crop Evolution*, **43**, 41-52

Guy G W, Whittle B A and Grey MJ
Dose dispensing Apparatus
GB Pat Application 25809.5, Oct 20, 2000

Guy G W, Whittle B A and Grey M J
Secure dispensing of materials
GB Patent Application 25811.1, Oct 20, 2000

Hampson A.J., Grimaldi M., Axelrod J. and Wink D. (1998)
Cannabidiol and (-) 9-Tetrahydrocannabinol are Neuroprotective Antioxidants
Proc. Nat. Acad. Sci. **95**, 8268-8273

Hardy *et al*
Respiratory Medicine (1993) **87**: 461-465

House of Lords Science and Technology Sub Committee report
The Development of Prescription Cannabis-Based Medicines (Jan 2001)

In-house Report GPA 002/000159
CBD Primary Screening Program (2000)

Iversen L.L.
The Science of Marijuana, Oxford University Press, 48-49 (2000)

Mechoulam R ed.
Cannabinoids as Therapeutic Agents, CRC Press, Boca Raton,FL, New York (1976)

Merck Index, 12th Edition, (1996) #1792

Merck's Manual (1899), Part 1, pg 26.

Pate D. US Patent Application Number 08/919317, 28 August 1997

Pertwee R.G. (1998)
Advances in Cannabinoid Receptor Pharmacology in Cannabis
The Genus Cannabis (Ed. Brown D.T.) Harwood Publishers, 125-174

Petro D.J. (1980)
Marijuana as a Therapeutic Agent for Muscle Spasm or Spasticity
Psychosomatics **21**(1), 81-85

Price M A P, and Notcutt W G
Cannabis in Pain Relief
In Cannabis : The Genus Cannabis (Ed Brown D T) Harwood Publishers, 223 - 246

Raman A.
The Cannabis Plant: Cultivation and Processing for Use
In Cannabis: the genus *Cannabis,* 29 – 54, Ed Brown D T

Ram and Sett (1982) Zeitschrift fur pflanzenphysiologie, **107**(1), 85-89

Samuelsson G
Drugs of Natural Origin 155-160Swedish Pharmaceutical Press, Stockholm, Sweden,

Smiley K.A., Karber R. and Turkanis S.A. (1976)
Effect of Cannabinoids on the Perfussed Rat Heart
Res. Comm. Chem. Pathol. Pharmacol, **14**, 659-673

Tashkin D P, Shapiro B J, and Frank I M
Acute pulmonary and physiological effects of smoked marijuana and oral delta-9-THC in healthy young men
N Eng J Med, **289**, 336-341

Touitou E
US Patent 5,540,934 (July 30, 1996)

Touitou E, Fabin B, Danny S and Almog S
Transdermal Delivery of Tetrahydrocannabinol
Int. J. of Pharmaceutics (1988) **43**: 9-15

Whittle B A and Guy G W

Formulations for sublingual delivery
GB Patent Application 103638.3, Feb 14, 2001

Zuardi A.W. and Guimares F.S. (1991)
Cannabidiol as an Anxiolytic and Antipsychotic in Cannabis: The Medicine Plant
McFarland & Co, London: 133-141

Claims

1. A pharmaceutical composition which comprises both the cannabinoids, cannabidiol (CBD) and tetrahydrocannabinol (THC) wherein the CBD is present in an amount by weight which is greater than the amount by weight of THC.

2. A composition as claimed in claim 1 wherein the ratio by weight of CBD to THC is greater than 2.5:1.

3. A composition as claimed in claim 1 or claim 2 wherein the ratio by weight of CBD to THC is between 99:1 to 2.5:1, preferably about 20:1 to about 2.5:1.

4. A composition as claimed in any one of the preceding claims wherein the ratio by weight of CBD to THC is about 19:1.

5. A composition as claimed in any one of claims 1 to 3 wherein the ratio by weight of CBD to THC is from about 5:1 to about 3:1.

6. A composition as claimed in any preceding claim which is free from cannabinoids other than CBD and THC.

7. A composition as claimed in claim 6 which is free from other cannabinoids found in *Cannabis sp.*

8. A composition as claimed in any one of the preceding claims wherein said CBD and THC are in substantially pure form.

9. A composition as claimed in any one of claims 1 to 5 which further comprises one or more other cannabinoids.

10. A composition as claimed in claim 9 wherein the one or more other cannabinoids are tetrahydrocannabinovarin (THCV) and/or cannabidivarin (CBDV).

11. A composition as claimed in any one of claims 1 to 5, 9 or 10 wherein the CBD and THC form part of an extract from a Cannabis plant, said extract comprising all the naturally occuring cannabinoids in said plant.

12. A composition as claimed in claim 11 wherein the Cannabis plant is selected from *Cannabis sativa, Cannabis indica,* the result of a genetic cross between them, a self-cross or a hybrid thereof.

13. A composition as claimed in claim 12 wherein the Cannabis plant is *Cannabis sativa*, subspecies *indica* and is selected from var. *indica* and var. *kafiristanica.*

14. A composition as claimed in any one of claims 11 to 13 which comprises extracts from two or more different Cannabis varieties wherein in the final composition the amount of CDB is greater than the amount of THC by weight.

15. A composition as claimed in any one of claims 11 to 14 wherein said extract is prepared by supercritical or sub-critical fluid extraction of dried Cannabis plant.

16. A method of preparing a Cannabis-based pharmaceutical composition which comprises CBD and THC in a pre-defined ratio by weight which method comprises the steps of :

a) providing at least one dried Cannabis plant variety for which the amount of CBD and THC by weight is known;

b) preparing an extract of said at least one Cannabis plant variety using at least one of the following procedures:

(i) maceration
(ii) percolation
(iii) extraction with solvent such as C_1-C_5 alcohols, norflurane or HFA227
(iv) subcritical or supercritical fluid extraction

c) formulating a material from said extract or extracts prepared in step (c) which exhibits said pre-defined ratio of CBD to THC; and

d) further formulating the product of step (c) into a pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

17. A method as claimed in claim 16 wherein prior to extraction said dried Cannabis is heated to a a temperature of from about 60°C to about 225°C, preferably about 100°C to about 150°C, to decarboxylate the acid form of any cannabinoids present in the extract.

18. A method as claimed in claim 16 or 17 which comprises extracting said at least one Cannabis plant variety with supercritical or subcritical CO_2.

19. A method as claimed in any one of claims 16 to18 wherein after extraction with said supercritical or subcritical fluid said extract is subjected to 'Winterisation' to remove waxes from the extract.

20. A method as claimed in any one of claims 16 to19 wherein the the amount by weight of CBD in the composition is greater than the amount by weight of THC.

21. A method as claimed in any one of claims 16 to20 wherein said pre-defined ratio of CBD to THC by weight is between 99:1 and 2.5:1, preferably about 20:1 to about 2.5:1.

22. A method as claimed in any one of claims 16 to 21 wherein said pre-defined ratio by weight of CBD to THC is about 19:1.

23. A method as claimed in any one of claims 16 to20 wherein said pre-defined ratio by weight of CBD to THC is from about 5:1 to 3:1.

24. A method as claimed in any one of claims 16 to19 wherein the composition comprises approximately equal amounts of CBD and THC by weight.

25. A method as claimed in any one of claims 16 to19 wherein the amount by weight of

THC in said composition is greater than the amount by weight of CBD.

26. A method as claimed in any one of claims 16 to19 wherein said pre-defined ratio by weight of CBD to THC is between 1:99 and 1:1.5.

27. A method as claimed in any one of claims 16 to 19 wherein said pre-defined ratio by weight of CBD to THC is about 1:39.

28. A method as claimed in any one of claims 16 to19 wherein said pre-defined ratio by weight of CBD to THC is about 1:2.

29. A method as claimed in any one of claims 16 to 28 wherein said composition is formulated for delivery nasally, sub-lingually, buccally, topically, orally, rectally, intravenously, intra-peritoneally, intra-muscularly, sub-cutaneously, transdermally, intra-vaginally, intra-urethrally, by nebulizer, as inhaled vapour or by installation directly into the bladder.

30. A method as claimed in any one of claims 16 to 28 wherein said composition is formulated to deliver CBD prior to delivery of THC and/or to provide a controlled release formulation.

31. A Cannabis-based pharmaceutical composition which is obtainable by the method of any one of claims 16 to 30.

32. A pharmaceutical composition which comprises both the cannabinoids tetrahydrocannabinovarin (THCV) and cannabidivarin (CBDV) wherein the CBDV is present in an amount by weight which is greater than the amount by weight of THCV.

33. A composition as claimed in claim 32 which further comprises CBD and/or THC.

34. A composition as claimed in claim 32 or 33 wherein the ratio by weight of CBDV to THCV is greater than 1.5:1.

35. A composition as claimed in any one of claims 32 to 34 wherein the ratio by weight of CBDV to THCV is from about 99:1 to about 1.5:1, preferably about 20:1 to about 2.5:1.

36. A composition as claimed in any one of claims 32 to 35 wherein the ratio by weight of CBDV to THCV is about 9:1.

37. A composition as claimed in any one of claims 32 to 35 wherein the ratio of CBDV to THCV by weight is from about 5:1 to 3:1.

38. A composition as claimed in claim 32 or any one of claims 34 to 37 which is free from other cannabinoids found in *Cannabis sp.*

39. A composition as claimed in any one of claims 32 to 38 wherein the CBDV and THCV form part of an extract from a Cannabis plant, said extract comprising all of the naturally ocurring cannabinoids in said plant.

40. A composition as claimed in claim 39 wherein the Cannabis plant is selected from *Cannabis sativa, Cannabis indica* or the result of a genetic cross between them, a self-cross or a hybrid thereof.

41. A modification of the method as claimed in any one of claims 16 to 30 wherein in step (a) at least one dried Cannabis plant variant is provided for which the amount of CBDV and THCV is known and a pharmaceutical composition is prepared comprising a pre-determined ratio by weight of CBDV to THCV instead of CBD and THC.

42. A pharmaceutical composition which comprises both the cannabinoids THC and THCV wherein the THCV is present in an amount by weight which is approximately equal to or greater than the amount by weight of THC.

43. A pharmaceutical composition as claimed in claim 42 wherein the the ratio by weight of THCV to THC is between 99:1 and 1.5:1

44. A composition as claimed in claim 42 or 43 wherein the ratio by weight of THCV to

THC is approximately 17:3.

45. A composition as claimed in any one of claims 42 to 44 which also comprises CBD and/or CBDV at an amount by weight which is less than the amount by weight of THCV.

46. A composition as claimed in any one of claims 42 to 45 wherein the THCV and THC form part of an extract from a Cannabis plant, said extract comprising all the naturally occurring cannabinoids in said plant.

47. A composition as claimed in claim 46 wherein said Cannabis plant is selected from *Cannabis sativa, Cannabis indica* or the result of a genetic cross between them, a self-cross or a hybrid thereof.

48. A modification of the method as claimed in any one of claims 16 to 30 wherein in step (a) at least one dried cannabis plant variant is provided for which the amount of THCV and THC is known and a pharmaceutical composition is prepared comprising a pre-determined ratio by weight of THCV to THC instead of CBD to THC.

49. A Cannabis-based pharmaceutical composition which is obtainable by the method of claim 41 or 48.

50. A pharmaceutical composition as claimed in any one of claims 1 to 15, 31 to 40, 42 to 46 and 49 for use in the treatment of inflammatory disease or any disease or condition during the course of which oxidative stress plays a part.

51. A pharmaceutical composition as claimed in claim 5 or 37 for use in the treatment of rheumatoid arthritis, or inflammatory bowel disease or Crohn's disease..

52. A pharmaceutical composition for use as claimed in claim 51 wherein in the composition the CBD and THC and/or the CBDV and THCV form part of an extract from a Cannabis plant. said extract comprising all the naturally occurring cannabinoids in said plant.

53. A pharmaceutical composition as claimed in 4 or 36 for use in the treatment of psychotic disorders, epilepsy, movement disorders, stroke, head injury, or diseases which require appetite suppression.

54. A pharmaceutical composition for use as claimed in claim 53 wherein in the composition the CBD and THC and/or CBDV and THCV form part of an extract from a Cannabis plant, said extract comprising all the naturally occurring cannabinoids in said plant.

55. A pharmaceutical composition obtainable by the method of claim 16 or 41and which comprises aapproximately equal amounts of CBD and THC or THCV and CBDV for the treatment of multiple sclerosis, spinal cord injury, peripheral neuropathy or other neurogenic pain.

56. A pharmaceutical composition which comprises a ratio by weight of THC to CBD or THCV to CBDV of from about 39:1 to about 99:1 for use in the treatment of cancer pain or migraine or for stimulation of appetite.

57. A pharmaceutical composition for use as claimed in claim 56 wherein the ratio by weight of THC to CBD or THCV to CBDV is approximately 39:1.

58. A pharmaceutical composition for use as claimed in claim 56 or 57 wherein in the composition the THC and CBD and/or THCV and CBDV form part of an extract from a Cannabis plant , said extract comprising all the naturally occurring cannabinoids in said plant.

59. The pharmaceutical composition of any of claims 42 to 46 for use in the treatment of cancer pain or migraine or for stimulation of the appetite.

60. Use of Cannabidiol (CBD) to extend the shelf-life of a pharmaceutical product which comprises one or more other biologically active components.

61. The use as claimed in claim 60 wherein the biologically active component is a

lipophilic substance.

62. The use as claimed in 60 wherein the biologically active substance is one of the classes of medicament shown in Table 3 other than cannabinoids.

63. The use as claimed in claim 60 wherein the biologically active substance is one of the medicaments shown in table 3 other than cannabidiol.

64. The use as claimed in claim 61 wherein the biologically active molecule is selected from cannabinol (CBN), cannabigerol (CBG), THC, CBDV and THCV.

65. A pharmaceutical composition substantially as described herein with reference to the accompanying Examples.

66. A method of making a pharmaceutical composition substantially as described herein with reference to the accompanying Examples.

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Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Other: ONLINE: CAS-ONLINE, EPODOC, JAPIO & WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
A	WO 02/069993A1	(FORSCHUNGSINSTITUT HISCIA VEREIN FÜR KREBSFORSCHUNG) See whole document, in particular Examples 1 and 2 and claims 1-14	
A	WP 02/064109A2	(GW PHARMA LIMITED) See whole document, in particular Example 5 and claim 26	
A	US2002111377A1	(STINCHCOMB) See whole document, in particular page 1, paragraph [0006]	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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